REMARKS

Claims 9, 11-17, and 21-58 remain pending and under examination in the case. No amendments are proposed at this time. All of the claims were rejected for obviousness and for nonstatutory, obviousness-type double patenting. These rejections are discussed below.

Rejection under 35 USC § 103 for obviousness

All of the claims are newly rejected under 35 USC § 103 as allegedly obvious in view of Carling (WO 93/11773; "Carling") in view of Roberts et al. (Thorax 49(11):1090-1095, 1994; "Roberts"). According to the Office action, Carling teaches that formoterol and budesonide can be used in combination to treat asthma, but does not expressly teach the treatment of COPD. The Office action goes on to say,

> Roberts et al. teach that bronchodilators and inhaled steroids, as anti-asthma drugs, alone or together were prescribed to patients with asthma, COPD and bronchitis.... Roberts et al. teach that of the 1605 patients diagnosed with COPD, 727 (equivalent to 45.3%) were prescribed both an inhaled steroid and an inhaled bronchodilator.... Roberts et al. teach that the prescribed bronchodilator included b2 agonist, and the inhaled steroids were beclomethasone or budesonide.
>
> It would have been obvious to skilled artisan to employ the Carling's medicament comprising formoterol and budesonide (b2-agonist, bronchodilator and inhaled steroid) in reducing the frequency and/or intensity of COPD since COPD and asthma are routinely treated and prescribed with inhaled steroids (budesonide) and b2 agonist having bronchodilating effects as taught by Roberts et al.

Applicants traverse.

As evidenced by the prior allowance of the claims (Notice of Allowance mailed October 5, 2007) after applicants overcame obviousness rejections based on Carling in combination with various other references, Carling says nothing about the usefulness of formoterol and budesonide to treat COPD, and in fact such use of the combination to treat COPD was not obvious in view of all of the prior art of record as of that date. Nothing in the newly cited Roberts article alters that conclusion.

Roberts investigated the prescribing rates for certain inhaled anti-asthma drugs in the UK, in order to determine how prescription rates for those drugs in different patient populations

varied among different practice groups in the U.K. The study group included patients diagnosed with asthma, COPD, or bronchitis. The inhaled drugs that had been prescribed to patients in the study included two inhaled steroids (beclomethasone and budesonide) and four bronchodilators (salbutamol, terbutaline, fenoterol, and salmeterol)[1], as well as two combination formulations: salbutamol/beclomethasone and fenoterol/iprotropium[2]. The data are summarized in Table 1 on page 1092 of Roberts. According to Table 1, a total of 3354 patients in the study had been diagnosed as having COPD (not the 1605 number cited in the Office action passage quoted above). Of the 3354 COPD patients, 1605 were prescribed inhalers of some sort, and 727 of those were given prescriptions for both a steroid and a bronchodilator. Thus, only 21.7% of the 3354 COPD patients (not 45.3% as cited in the Office action) were prescribed both a steroid and a bronchodilator in separate prescriptions. Table 1 does not break down the numbers to reveal which type of steroid and which type of bronchodilator was prescribed. Thus, Roberts does not give the reader any idea how many (if any) of the 21.7% received a prescription for budesonide as the steroid, and how many were prescribed beclomethasone instead. It is entirely possible that every one of the 21.7% was given a prescription for beclomethasone, and *none* was prescribed budesonide, with recipients of budesonide prescriptions limited to some of the asthma patients that made up the vast bulk of the patients in this overall study. Furthermore, *none* of the patients is reported as having received a prescription for formoterol, a drug that was not even approved for marketing in the U.K. at the time of the study. Clearly, the limited teachings of Roberts are not particularly relevant to the question of whether a physician of ordinary skill in the art would have been motivated to prescribe *budesonide* and *formoterol* for treatment of COPD, whether in separate inhalers or together in one.

It is also instructive to note that, even though at least two different inhaler products containing combinations of drugs were available during the time period covered by the Roberts study (see the footnote below Table 1 of Roberts), apparently only 50 COPD patients out of the 3354 total (i.e., only 1.5%) were given a prescription for such a combination inhaler. (See Table 1, the line designated "Combination preparation.") In contrast, a total of 1555 COPD

[1] Page 1091, first column, second paragraph
[2] Page 1092, footnote under Table 1

patients[3] (i.e., 46%) were given prescriptions for either a steroid inhaler alone or a bronchodilator inhaler alone, or both drugs in separate inhalers; and 1391 (i.e., 41%) were not given any therapy at all. These statistics would appear to indicate that there was little enthusiasm for treating COPD with the available combination products, even though each would presumably have the same advantage of being "conveniently in the same inhaler" that the Office action cites as a motivation to use the Carling combination inhaler (see Office action at page 4). One possible factor influencing physicians' apparent avoidance of the combination products in the Roberts study may have been that a combination product would not permit different frequency and/or timing of administration of the two drugs, requiring the patient always to take both at the same time in a fixed ratio, even if one of the drugs may be needed more often than the other or in varying amounts. Such an inherent disadvantage would apply to *any* combination inhaler product, including the combination taught by Carling.

The numbers reported by Roberts in Table 1 suggest that physicians polled in the study vastly favored either not prescribing anti-asthma drugs at all in treating COPD (41%), or prescribing only a single drug (24.7%), or prescribing two separate inhalers, each with a single drug (22.7%), and strongly disfavored use of a combination inhaler (1.5%). Applicants submit that this amounts to a *teaching-away* from use of a combination inhaler of any sort. It certainly does not indicate that one of ordinary skill in the art would have had a motivation to try the Carling combination inhaler in treatment of COPD, much less an expectation of success.

As further evidence of teachings-away in the art, applicants note that those of skill in the art had repeatedly investigated whether inhaled budesonide treatment was useful for COPD patients, and in every case determined that it produced little if any benefit (in marked contrast to the significant benefit this drug provides for asthma patients). See, for example, Renkema, Chest 109:1156-1162, 1996, and Smeenk *et al.*, Nederlands Tijdschrift voor Geneeskunde 140:94-98, 1996, which were extensively discussed at pages 10-12 of the Appeal Brief filed in the present case on March 7, 2007 (the "Appeal Brief"). Also of interest are Watson *et al.,* Chest 101:350-355, 1992 (reference B7 in the enclosed Information Disclosure Statement), and Wempe *et al.*,

[3] 77 + 751 + 727 = 1555

Thorax 47:616-621, 1992 (reference B8 in the enclosed Information Disclosure Statement). Watson *et al.* showed that, consistent with previous studies with budesonide in COPD, a relatively high dose of inhaled budesonide (1200 μg per day) did not improve lung function in smokers with mild airflow obstruction, and did not improve response to either of two bronchodilators (salbutamol and ipratropium bromide). See the abstract at page 350. Likewise, Wempe *et al.* found that even higher doses (1600 μg per day) of inhaled budesonide had no significant effect on lung function in COPD patients (page 619, first column), and did not improve the patients' response to the same two bronchodilators (page 619, first column, and page 620, Figure 3). Given these *teachings-away* in the art, there would have been no incentive to use budesonide to treat COPD, whether alone or in combination with a bronchodilator, and certainly no expectation of success upon doing so. As emphasized by the U.S. Supreme Court in *KSR v. Teleflex,* 127 S.Ct. 1727 (2007), a teaching-away in the art has long been considered highly relevant evidence of nonobviousness. Applicants have provided several examples of such teachings-away. Since none of the art cited by the Examiner contradicts these teachings-away by showing that budesonide (whether alone or in combination with a bronchodilator) is indeed useful for treating COPD, applicants maintain that they stand as uncontroverted proof of nonobviousness.

As still another basis for withdrawal of the rejection of the claims, Appellants note the extensive evidence of surprising results of record in this case. It is not clear whether the Examiner has taken that evidence into account in formulating the present rejection, though the statement at page 4 of the Office action regarding an unidentified "Applicants' declaration" may be a reference to this evidence of record. According to the Office action at page 4,

> Applicants' declaration has been carefully reviewed and reconsidered. However, it is not found to be persuasive because Robert et al. teach that the respiratory conditions such as COPD and asthma are routinely treated and prescribed with inhaled steroids (budesonide) and bronchodilator having b2 agonistic activity such as formoterol.

Applicants note that, contrary to the above-quoted assertion, Roberts et al. does NOT teach that COPD is routinely "treated and prescribed" with inhaled budesonide. Roberts et al. says at page 1091 that the "steroids" prescribed for asthma, COPD and bronchitis patients in the study

were beclomethasone and budesonide, but nowhere states that COPD patients in particular received prescriptions for budesonide. Table 1 of Roberts et al. uses the generic term "steroid," and does not specify whether the steroid prescribed for the COPD patients was solely beclomethasone, solely budesonide, or some of each. One cannot conclude from the data in Roberts et al. that even a single COPD patient was treated with budesonide. It is quite possible that only asthma patients (which made up the large majority of the patients included in the study) received prescriptions for both budesonide and beclomethasone, while the steroid prescribed for COPD patients may have been only beclomethasone. To draw any definitive conclusions from the limited information in Roberts is plainly not warranted.

The above-quoted statement from the Office action is also misleading in its implication that Roberts teach that COPD is "routinely treated and prescribed" with the bronchodilator formoterol. Formoterol is not even mentioned in this reference, much less said to be "routinely treated and prescribed."

The Examiner also attempts to rely on Carling as additional justification for her position that applicants' results are not surprising, asserting at page 4 of the Office action:

> Further, Carling et al's combination comprising budesonide and formoterol has a greater efficacy[4] and duration of bronchodilation action. Therefore, the greater efficacy and duration of bronchodilation action is also expected in the patients in obvious treatment of COPD upon the employment of the Carling's medicament.

As previously established by applicants' Appeal Brief, Carling is focused entirely on treatment of asthma and asthma-like conditions, of which COPD is not one. The Appeal Brief at page 8 cited a 2003 editorial[5] (published long after the present application's 1997 priority date) as repeatedly emphasizing that asthma and COPD are "fundamentally different" diseases that are unlikely to be successfully treated the same way. Other evidence described in the Appeal Brief at pages 8-9 also supports the distinction between asthma and COPD. Thus, the teachings of

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[4] Applicants note that the word actually used by Carling at page 4 is "efficiency," not "efficacy." As the two words are quite different in meaning, Applicants respectfully request acknowledgement by the Examiner and correction of the record on that point.

[5] K.F. Rabe (*Eur. Respir. J.* 22:874-875, 2003)

Carling regarding what is helpful in treating asthma offers no guidance whatsoever to one seeking a treatment for COPD. Carling provides no clue that either budesonide or formoterol might be useful in treating COPD, and certainly does not suggest that the two drugs in combination would interact synergistically to combat the symptoms of this deadly disease.

Given the utter lack of any teaching in Roberts that COPD is routinely treated with either budesonide or formoterol, much less with a combination thereof, and the utter lack of any suggestion in Carling that the combination of budesonide and formoterol produces a synergistic effect in COPD or any other non-asthma condition, the Examiner's entire basis for dismissing applicants' evidence of surprising results disintegrates. Furthermore, even if the Examiner's interpretation of Roberts and Carling were correct, that would still not justify wholesale dismissal of the dramatic evidence of surprising and synergistic results provided by applicants. Nothing in either cited reference gives any reason to expect the striking results in COPD found by applicants, particularly in view of the many prior clinical studies (discussed above) that found budesonide to be of little or no value in treating COPD, despite its well-established usefulness in treating asthma. Applicants therefore urge the Examiner to reconsider her position. To aid the Examiner in doing so, applicants summarize some of the evidence of record below, focusing on the graphs attached as Appendices 1-9 to the Declaration of Jan Trofast originally submitted November 4, 2005 (the "2005 Trofast Declaration"), and the publication by Calverley *et al.* (*Eur. Resp. J.* 22:912-919, 2003). These materials were included as Items 8 and 9, respectively, in the Evidence Appendix of the Appeal Brief.

The graphs submitted as Appendices 1-9 with the 2005 Trofast Declaration illustrate data collected from a placebo-controlled 12-month clinical trial that was performed using a combination of budesonide/formoterol fumarate dihydrate (under the product name Symbicort®) in the treatment of moderate to severe COPD. Before randomization, 1022 patients were treated in a 2 week initial run-in period with oral prednisolone (30 mg once daily), inhaled formoterol fumarate dihydrate ("FFD", marketed under the brand name Oxis®; 2 puffs twice per day, each

puff delivering 4.5 μg FFD to the patient from a metered dose[6] of 6.0 μg FFD), and terbutaline as needed (Bricanyl®; 0.5 mg by inhalation). All of the following medications and the placebo were delivered from a Turbuhaler® inhaler. The patients were randomized into four groups and treated as follows:

Group 1: Budesonide/FFD combination (Symbicort®; 2 puffs twice per day, each puff delivering 160 μg budesonide/4.5 μg FFD to the patient (corresponding to a metered dose of 200 μg budesonide and 6.0 μg FFD for the monoproducts))

Group 2: Budesonide alone (marketed under the brand name Pulmicort®; 2 puffs twice per day, each puff delivering 160 μg budesonide to the patient from a metered dose of 200 μg budesonide)

Group 3: FFD alone (Oxis®; 2 puffs twice per day, each puff delivering 4.5 μg FFD to the patient from a metered dose of 6.0 μg FFD)

Group 4: Inhaled placebo composition (2 puffs, twice daily, no active ingredients)

The patients were studied for 12 months, with various measures of COPD symptoms being regularly recorded. The results of this study suggest that the combination of budesonide and FFD (*i.e.*, formoterol) produces quite pronounced synergistic effects by not just one, but *several* different measures—any ***one*** of which is sufficient to establish that the claimed methods produce surprisingly beneficial results.

First, as shown in the graph titled "Symbicort reduces the risk of first exacerbation requiring medical intervention"[7] (Appendix 1 attached to the 2005 Trofast Declaration), the hazard rate was reduced (compared to placebo) by **28.5 %** in patients treated with the budesonide/FFD combination. The corresponding reduction for patients treated with budesonide

[6] A "metered dose" is the amount of product that is positioned in the inhaler for delivery to the patient with each puff. Not all of the metered dose is delivered to the patient; some product will stick to the sides of the inhaler, or will otherwise remain in the inhaler. A "delivered dose" is the amount of product that exits the inhaler. This amount is less than the metered dose.

[7] Severe exacerbations were considered to be exacerbations requiring medical intervention, *i.e.*, administration of antibiotics and/or oral steroids, and/or hospitalization due to respiratory symptoms.

alone was **7.5 %**, while FFD alone actually produced an increase (compared to placebo) of **1.5 %**. A merely additive effect would have produced a 6.0 % reduction[8]. Thus, it is clear that the combination product produced a synergistic effect. *If the Examiner intends to maintain the rejection, she is asked to address why she believes these particular synergies were entirely predictable in view of the art.*

Second, the graph titled "Symbicort reduces the number of severe exacerbations/patient/year" (Appendix 2 attached to the 2005 Trofast Declaration) also strongly implies a synergistic effect of the budesonide/FFD combination therapy. As compared to treatment with placebo, treatment with FFD alone actually increased the number of exacerbations per patient per year slightly (**+3%**), while treatment with budesonide alone decreased the number of exacerbations per patient per year by **12%**. **Patients treated with the budesonide/FFD combination, however, exhibited a 24% reduction in exacerbations.** This result demonstrates a synergistic effect, as the 24% reduction is much greater than the 9% reduction expected if the effect of the combination therapy were merely additive. *If the Examiner intends to maintain the rejection, she is asked to address why she believes these particular synergies were entirely predictable in view of the art.*

Third, a synergistic effect was also indicated in the patients' need for oral steroids during the course of the study, as shown in the graph titled "Symbicort reduces need for oral steroids" (Appendix 3 attached to the 2005 Trofast Declaration). Treatment with budesonide alone reduced the hazard rate of time to first oral steroid use by **14%** compared to placebo, and treatment with FFD alone reduced the hazard rate by **13%** as compared to placebo. **In contrast, treatment with the budesonide/FFD combination reduced the hazard rate of time to first oral steroid by 42.3% versus placebo.** This is far better than the 27% reduction that would have been expected from an additive effect of the individual budesonide and FFD components. *If*

[8] In order to assure the stability of the first order approximation used above to assess the additive effects, a fully elaborated approach is also presented. By treating these data in a multiplicative way (the model being relative), the additive effect of budesonide and formoterol is = 100 – (100-7.5)*(100+1.5)/100 = 6.1 % and the effect of the combination (Symbicort®) over this is = 100 - 100*100*(100-28.5)/((100-7.5)*(100+1.5)) = 23.8 %. Note that this effect is even greater than suggested above (= 28.5-6.0 = 22.5 %), showing that calculation on the additive scale gives a conservative estimate.

the Examiner intends to maintain the rejection, she is asked to address why she believes these particular synergies were entirely predictable in view of the art.

Fourth, a synergistic effect was also observed in the effect on night awakenings, as shown in the graph titled "Symbicort increases nights without awakenings" (Appendix 4 attached to the 2005 Trofast Declaration). Treatment with either budesonide alone or FFD alone resulted in an adjusted mean change in awakenings-free nights of **+3.7 %** (compared to placebo). If budesonide and FFD in combination had a merely additive effect on the change in awakenings-free nights, the adjusted mean change of the combination therapy (compared to placebo) would be expected to be **+7.4 %.** However, treatment with the combination therapy resulted in an adjusted mean change in awakenings-free nights (compared to placebo) of **+ 9.2 %,** even greater than the calculated additive effect of 7.4 %. *If the Examiner intends to maintain the rejection, she is asked to address why she believes these particular synergies were entirely predictable in view of the art.*

Fifth, a synergistic effect was also indicated in the morning peak expiratory flow (PEF), as shown in the graph titled "Symbicort rapidly improves and maintains morning PEF" (Appendix 5 attached to the 2005 Trofast Declaration). The difference in adjusted mean change of morning PEF, as compared to placebo, was **3.5** L/min for the patients treated with budesonide alone, **11.1** L/min for those treated with FFD alone, **and 18.3 L/min for the patients treated with the budesonide/FFD combination**, *i.e.*, 3.7 L/min higher than would be expected if the effect were merely additive. These data were presented previously in the declaration of Christer Hultquist, filed December 13, 2002 (Item 7 in the Evidence Appendix), and supplement the data presented in Calverley *et al.* at page 915, column 2, and in Figure 3(a) at page 916. *If the Examiner intends to maintain the rejection, she is asked to address why she believes these particular synergies were entirely predictable in view of the art.*

Sixth, the graph titled "Symbicort rapidly improves and maintains evening PEF" (Appendix 6 attached to the 2005 Trofast Declaration) strongly implies a synergistic effect on the patients' evening peak expiratory volume (PEF). The difference in adjusted mean change of evening PEF, as compared to the placebo, was **2.0** L/min for the patients treated with budesonide

alone, **8.9** L/min for those treated with FFD alone, and **14.1 L/min for the patients treated with the budesonide/FFD combination**, *i.e.,* 3.2 L/min higher than would be expected if the effect of the budesonide/FFD combination were merely additive. *If the Examiner intends to maintain the rejection, she is asked to address why she believes these particular synergies were entirely predictable in view of the art.*

Seventh, the graph titled "Symbicort produces rapid and maintained improvement in lung function (FEV1)" (Appendix 7 attached to the 2005 Trofast Declaration) illustrates that FEV1 decline was less severe in patients treated with a budesonide/FFD combination therapy than in those treated with either monotherapy. The combination therapy was **14%** better than placebo in this regard, while the monotherapies were only **8%** and **2%** better than placebo. Also, as illustrated by the graph titled "Symbicort improves health related quality of life, HRQL" (Appendix 8 attached to the 2005 Trofast Declaration), the mean change in total score on St. George's Respiratory Questionnaire (SGRQ) as compared to placebo was **-7.5**, which was a greater improvement than that observed following treatment with budesonide alone (**-3.0**) or FFD alone (**-4.1**)[9]. *If the Examiner intends to maintain the rejection, she is asked to address why she believes these particular synergies were entirely predictable in view of the art.*

Finally, as illustrated by the graph titled "Symbicort reduces discontinuations compared to other treatments" (Appendix 9 attached to the 2005 Trofast Declaration), fewer patients withdrew from the study when they received the budesonide/FFD combination therapy than when they received either of the monotherapies. These data supplement the data in Table 1 of Calverley *et al.* at page 914, which reports that **71%** of the patients originally enrolled in the study and who received treatment with the combination of budesonide and FFD completed the study. By comparison, only **59%** of patients receiving placebo completed the study, approximately the same as those receiving FFD alone (**56%**) or budesonide alone (**60%**). The multiple beneficial effects described above may have contributed to the fact that fewer patients receiving the budesonide/FFD combination therapy withdrew from the study. *If the Examiner*

[9] A change of *minus* 4 points in the SGRQ represents a clinically important improvement in health related quality of life. The more negative the score, the better the quality of life.

intends to maintain the rejection, she is asked to address why she believes these particular synergies were entirely predictable in view of the art.

Applicants submit that the above clinical evidence is proof, *many times over*, that the presently claimed methods produce results that could not have been predicted from anything in the art. Each of these separate observations of synergistic effects was unexpected and thus important, objective evidence of nonobviousness. Each is individually sufficient to establish nonobviousness; taken together, the evidence is overwhelming. Under U.S. law, any objective indicia of non-obviousness, such as surprising results, must be taken into account when considering whether the claims are obvious over prior art. Though the Examiner claims to have duly considered the data, the fact that she found it "unpersuasive" merely because Carling mentions that the same combination of drugs has "greater efficiency and duration of bronchodilator action" in treating an entirely different condition suggests that she did not seriously take the data into account. Carling provides no indication that one could expect the dramatic effects of record in the present case in relation to COPD.

The court in In re Soni, 54 F.3d 746, 751 (Fed. Cir. 1995), stated that "when an applicant demonstrates *substantially* improved results…and *states* that the results were unexpected, this should suffice to establish unexpected results *in the absence of* evidence to the contrary." (Emphasis in original). Applicants have presented such results and stated that they were unexpected. (See, *e.g.*, page 5 of the March 1, 2004, Trofast Declaration, Item 4 in the Evidence Appendix attached to the Appeal Brief, in which Dr. Trofast described the results presented in Calverley *et al.* showing the effect of the combination of formoterol and budesonide to reduce the frequency of COPD exacerbations as **"surprising given the low efficacy or ineffectiveness of treatment with either budesonide or formoterol alone."** The Examiner has failed to provide any legitimate "evidence to the contrary," as required by In re Soni. Therefore, applicants' evidence of unexpected results must be given due weight as cogent and persuasive evidence of nonobviousness.

As a final, independent ground for establishing the nonobviousness of the claimed methods, applicants remind the Examiner of the substantial evidence of record concerning

skepticism of experts, one of the standard objective indicia of nonobviousness recognized under U.S. law (see, *e.g.*, Graham v. John Deere, 383 U.S. 1 (1966)). See, for example, the editorial by K.F. Rabe discussed above and in the Appeal Brief. This editorial shows that, *even in 2003, long after the present application's 1997 priority date,* an expert in the field of respiratory disease repeatedly asserted that COPD and asthma are fundamentally different diseases that are unlikely to be successfully treated the same way. Though this expert said he was "happy to adopt" use of formoterol/budesonide combination therapy for treatment of asthma, **he was skeptical that the combination could be generally useful in treatment of COPD.** That the author could still be skeptical in 2003, following publication of two clinical trials disclosing the benefits of the combination therapy in COPD, suggests how entrenched the assumption was that these drugs (or at least budesonide) would have no value in treating COPD. Another post-filing date article (Vestbo et *al., Lancet* 353:1819-1823, 1999; Item 10 in the Evidence Appendix attached to the Appeal Brief) flatly states in the abstract, **"Inhaled budesonide was of no clinical benefit in COPD patients recruited from the general population by screening. We question the role of long-term inhaled corticosteroids in the treatment of mild to moderate COPD."** It is clear from such post-filing date evidence that the art was skeptical that budesonide alone or in the claimed combination therapy was of any value in treating COPD, even years after applicants' priority date. The Examiner has not explained why something about which the experts in the art were clearly skeptical would have been "obvious" to her.

In summary, Appellants have established

1. that the cited art provided neither motivation to carry out the claimed methods, nor expectation of success upon doing so;
2. that the art actually taught away from the claimed methods;
3. that administration of the claimed combination produces unexpected and synergistic results; and
4. that the bias in the art against the usefulness of inhaled corticosteroids in treating COPD was so pronounced that it remained even years after applicants' filing date.

Any one of these points would be sufficient to mandate withdrawal of the rejection. Taken together, the weight of the evidence is overwhelming.

In addition to the above arguments and evidence, which apply to all of the claims, applicants note that various independent and dependent claims include limitations that provide further grounds for distinguishing the art. These claims are discussed in two groupings below (groupings I and II). A few claims contain limitations appropriate to both of these groupings, so are discussed in both.

I. Claims 9, 11-17, 21-40, 50 and 54

Each of these claims specifies that the method "is effective to reduce the frequency and/or intensity of [COPD] exacerbations in the patient" (claim 9 and its dependents) or "produces a reduction in frequency or intensity of COPD exacerbations in the patient" (claims 50 and 54). Neither Roberts nor Carling even mentions COPD exacerbations. The Examiner has pointed to nothing in the art that would have led one of ordinary skill to believe that either formoterol or budesonide would be effective for this purpose. In fact, Renkema (Chest 109:1156-62, 1996; "Renkema"), which is of record and was discussed at length in the Appeal Brief, found that budesonide alone is not useful for reducing the frequency or duration of exacerbations in COPD patients. See Renkema at page 1160, left column. Given this *teaching-away* in the art, applicants submit that one of ordinary skill would not have been motivated to try budesonide in combination with any other drug for the purpose of reducing exacerbation frequency and/or intensity, as required by pending claims 9, 11-17, 21-40, 50 and 54—and certainly would not have had any reasonable expectation of success even if the experiment had been attempted. This is yet another basis for withdrawing the rejection with respect to these claims.

II. Claims 28, 34, 36, 38, 40, 43, 46, 53, and 56-58

Neither Roberts nor Carling teaches use of formoterol and budesonide for treatment of COPD, so *a priori* neither teaches what dosage would be effective for COPD. Claims 28, 34, 36, 38, 40, 43, 46, 53, and 56-58 specify particular daily doses or daily dose ranges of budesonide. For claims 28, 34, 36, 43, and 56-58, the maximal dose of budesonide is 640 µg/day, while for claims 38, 40, 46, and 53, the maximal dose is just 320 µg/day. As explained in the Appeal Brief at pages 21-22, Renkema taught that even a high dose of 1600 µg/day of budesonide was of little value in treatment of COPD, and that, if anything, still higher doses might be necessary. The Examiner has not pointed to any prior art disclosure that would contradict Renkema's *teaching away* and establish that, despite Renkema's negative results, one of ordinary skill in the art would nevertheless have expected a dose of budesonide much lower than the 1600 µg/day tested by Renkema (e.g., 640 µg/day or less, or 320 µg/day or less) to be effective in treating COPD when combined with formoterol. Thus, claims 28, 34, 36, 38, 40, 43, 46, 53, and 56-58 are nonobvious and patentable over the combination of Roberts and Carling for yet another reason.

Rejections for nonstatutory, obviousness-type double patenting

The Office action at pages 5-8 alleges that all of the presently pending claims are unpatentable for obviousness-type double patenting over certain claims of each of US Patent Nos. 5,674,860, 5,972,919, and 6,030,604, all when taken in view of Roberts. Applicants traverse. Each of the rejections is discussed below.

Rejection over claims 17-36 of US Patent No. 5,674,860, in view of Roberts

US Patent No. 5,674,860 contains the same disclosure as WO 93/11773 (Carling), the reference cited in the above obviousness rejection. Applicants have established above that the presently claimed methods of treating COPD are not obvious in view of Carling and Roberts, even where the entire disclosure of Carling is taken into account. Where, as here, only certain claims derived from the Carling disclosure are combined with Roberts, applicants' position regarding nonobviousness is, if anything, even stronger. Applicants have pointed out teachings-away in the art, have provided voluminous evidence of surprising results, and have demonstrated

that, even after publication of applicants' clinical results, experts in the field remained highly skeptical that COPD could be treated with a budesonide/formoterol combination, even though it was well established by the present priority date that the combination worked for asthma. In view of all of this objective evidence, the presently claimed methods cannot be deemed to be mere obvious variations of the claims of the cited patent. Withdrawal of the rejection is therefore requested.

Rejection over claims 3-5, 9-12, and 15-19 of US Patent No. 5,972,919, in view of Roberts

US Patent No. 5,972,919 contains the same disclosure as WO 93/11773 (Carling), the reference cited in the above obviousness rejection. Applicants have established above that the presently claimed methods of treating COPD are not obvious in view of Carling and Roberts, even where the entire disclosure of Carling is taken into account. Where, as here, only certain claims derived from the Carling disclosure are combined with Roberts, applicants' position regarding nonobviousness is, if anything, even stronger. Applicants have pointed out teachings-away in the art, have provided voluminous evidence of surprising results, and have demonstrated that, even after publication of applicants' clinical results, experts in the field remained highly skeptical that COPD could be treated with a budesonide/formoterol combination, even though it was well established by the present priority date that the combination worked for asthma. In view of all of this objective evidence, the presently claimed methods cannot be deemed to be mere obvious variations of the claims of the cited patent. Withdrawal of the rejection is therefore requested.

Rejection over claims 1, 2, 9, and 14-16 of US Patent No. 6,030,604, in view of Roberts

The Office action asserts at pages 7-8 that the instant claims differ from claims 1, 2, 9, and 14-16 of US Patent No. 6,030,604 ("'604") solely in that the instant claims are drawn to treatment of COPD. Applicants point out that this simply is not true—there are a number of other distinctions in addition to that one. For example, unlike all of the instant claims, claims 1 and 2 of '604 are drawn to compositions, not methods of treatment. Unlike all of the instant

claims, claims 1, 9, 14 and 16 of '604 do not specify that budesonide is part of the composition. Unlike all of the instant claims, claims 1, 9, 14, and 15 do not specify that formoterol is part of the composition. Thus, none of the instant claims could be said to be obvious variations on the '604 claims, even in view of Roberts. The '604 claims are therefore even less pertinent than the claims of the two other patents discussed above, US Patent Nos. 5,674,860 and 5,972,919. When one considers the additional limitations in many of the instant claims, the distinctions over the '604 claims is even more marked. Note, for example, the limitation in instant claims 9, 11-17, 21-40, 50 and 54 regarding reducing the frequency and/or intensity of COPD exacerbations, a topic that is not mentioned in Roberts or in the '604 claims. Also note the limitations in instant claims 28, 34, 36, 38, 40, 43, 46, 53, and 56-58 regarding dosage of budesonide. Given the teachings in the prior art (e.g., Renkema) that even high doses of budesonide were of little value in treating COPD, clearly one of ordinary skill would not have considered the relatively low doses required by claims 28, 34, 36, 38, 40, 43, 46, 53, and 56-58 to have been "obvious" to use for treating COPD. Applicants have pointed out teachings-away in the art, have provided voluminous evidence of surprising results, and have demonstrated that, even after publication of applicants' clinical results, experts in the field remained highly skeptical that COPD could be treated with a budesonide/formoterol combination, even though it was well established by the present priority date that the combination worked for asthma. In view of all of this objective evidence, the presently claimed methods cannot be deemed to be mere obvious variations of the claims of the cited patent. Withdrawal of the rejection is therefore requested.

CONCLUSION

Applicants respectfully ask that all of the rejections of record be withdrawn and the claims allowed. If any issues remain, the Examiner is asked to telephone the undersigned to discuss.

Please apply the fees of $130.00 for the Petition for One Month Extension of Time and $180.00 for the Information Disclosure Statement, and any other charges or credits, to deposit account 06-1050, referencing Attorney Docket No. 06275-0150003.

Respectfully submitted,

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